Pharmacology of oxygen

By Alex Yartsev - 04/06/2018
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This chapter is related to the aims of Section F11(i) from the 2023 CICM Primary Syllabus which expects the exam candidate to *"describe the pharmacology of oxygen"*. In spite of being a vitally important metabolite and an essential ingredient of normal multicellular life, oxygen is nonetheless not excused from being treated as a drug, with side effects and contraindications. Given that virtually all patients in the ICU end up receiving oxygen, it seems reasonable to expect the competent ICU trainee to be intimately familiar with its properties, as it would probably be irresponsible to funnel litres of something into one's patients while knowing nothing about its effects.

Unlike much of what Deranged Physiology offers, this topic has exam relevance for the CICM Part I exam candidates. Question 1 from the first paper of 2011 asked about the physiological consequences of breathing 100% oxygen at sea level; also Question 6 from the first paper of 2009 and Question 14 from the first paper of 2023 asked them to *"describe the pharmacology of oxygen"*, in a rare outburst of good construct alignment. Weirdly, the examiners commented with what seems like approval on the fact that *"most candidates mentioned the oxygen is an odourless and colourless gas"*. Judging by the rest of the college comments, the expectations were that the trainees would discuss the pharmacokinetics of oxygen, its metabolism, its effects on the circulation, its clinical uses beyond the reversal of hypoxia, and the responses of various body systems to hyperoxia. This chapter will attempt to summarise this material for rapid cheek-pouch storage and exam regurgitation. The need to integrate numerous fascinating sources has completely disengaged the author's already weakened inhibitory mechanisms, such that the end of this summary has proliferated uncontrollably into a poorly differentiated mass of apocryphal material. The time-poor candidate would be well advised to limit their revision to the grey box offered below.

In brief summary:

Physico-chemical properties of oxygen

- Oxygen (O_2)is a diatomic gas with a density and viscosity slightly higher than that of air.
- Conventional "wall" oxygen is delivered at approximately 4 atmospheres of pressure (415 kPa) and is close to 0℃ at the wall outlet.

Administration:

- As an inhaled agent via a selection of fixed or variable performance delivery devices
- As intravenous or intra-arterial infusion of well-oxygenated blood (i.e. ECMO)
- Externally (as in hyperbaric oxygen therapy)

Absorption:

- Pulmonary absorption (250ml/min with 21% FiO_2, at rest)
- Cutaneous absorption (under 1ml/min at normal atmospheric pressure)
- Oral (and other) mucosal absorption (usually, nil)

Metabolism

- Metabolised in all tissues (mainly brain, heart and skeletal muscle)
- Mainly metabolised by cytochrome c mitochondrial enzymes (90%)
- Zero-order clearance kinetics, roughly 200ml/minute
- Main metabolites are CO_2 and H_2O, cleared via the lung and renally.

Indications for use

- Supplementation (in hypoxemia)
- Prophylaxis (in pre-oxygenation for anaesthesia)
- As an antidote (carbon monoxide toxicity)
- Therapeutic uses:
  - As an antibiotic (hyperbaric oxygen for deep anaerobic infections)
  - To decrease the volume of air-filled body cavities by denitrogenation (eg. pneumothorax and pneumoencephalus)
  - In management of decompression sickness

Contraindications

- Bleomycin use (leads to pulmonary fibrosis)
- Paraquat toxicity (worsens ARDS)
- Aspiration of acid (worsens ARDS)

Complications

- Drying of mucous membranes and inspissation of secretions
- Inflammatory tracheobronchitis
- Decreased central respiratory drive (minimally)
- Hypecapnoea in "CO_2 retainers" mainly by virtue of V/Q mismatch and Haldane effect
- Absorption atelectasis
- Increased left-to-right shunting in ASDs
- Increased peripheral vascular resistance
- Cerebral and coronary vasoconstriction
- Euphoria
- Retrolental fibroplasia of the newborn
- Decreased erythropoiesis

Toxicity

- Visual changes and seizures (hyperbaric)
- Toxicity from free radicals (worsening ARDS)

Caveats

- Few uses are evidence-based
- Evidence does not support the use of supraphysological oxygen in most cases, i.e. hyperoxia is discouraged.

Now, in some detail. There are some excellent resources for this topic. The college answer to Question 6 makes reference to Nunn's Respiratory Physiology, but does not reference it very well . Which edition? Which chapter? In the 8th edition, Chapter 10 (p. 169) deals with the properties of oxygen. Another possible high-level authoritative source is Chapter 28 from the 7th edition of Oh's Manual (*Oxygen therapy*, p. 327 by Adrian J Wagstaff) , the reasons for mentioning it being the possibility that perhaps the editors or the author were/are involved in writing CICM Part I questions. For

the freegan, the British Thoracic Society Guidelines (O'Driscoll et al, 2017) is more detailed and purposeful than either of the aforementioned resources. An awesome article on oxygen toxicity is Chawla & Lavania (2001), written for the Medical Journal of the Armed Forces of India. For some exotic indications Haim Bitterman's 2009 article, "Bench-to-bedside review: oxygen as a drug" has some discussion of the rationale for hyperoxia, where oxygen is used as a therapy rather than as a supplement. For those unwilling to odyssey through some 200 pages of references, the answer to Question 6 could be written quite well after skimming though the excellent LITFL entry on oxygen.

Chemical properties and molecular structure

It is reasonable, when posed with the question "what are the properties of a gas", to mention its smell and colour. Not all gases are colourless and odourless like oxygen (eg. sublimated gaseous iodine is purple and smells like pool chlorine). When chilled, liquid oxygen takes on a beautiful blue hue, which is due to the fact that it absorbs light avidly at the red and green parts of the visible spectrum (Ogryzlo et al, 1965).

- **Melting point:** −219 ℃
- **Boiling point** −183 ℃
- **Density:** 1.429 g/L (at STP)
- **Viscosity:** 204 μP (poise)

By comparison, the density of air is around 1.18g/L, and its viscosity is around 184 μP. This has implications regarding where one would prefer to be in a large relatively hypoxic chamber (the floor, of course - where else would a hypoxic person be). The higher viscosity favours the movement of oxygen through smooth tubes (laminar flow). It flows fine until it gets to your branching asthmatic airways, and then with increasing turbulence the resistance grows exponentially.

The solubility of oxygen in water is generally quite poor, 0.03ml/L/mmHg. Thus, at normal atmospheric pressure, at physiological PAO_2 there is only about 3ml of oxygen in every litre of optimally oxygenated body water, and 100% FiO_2 will translate into a maximum body water oxygen content of only about 22.8ml/L.

Oxygen in nature is an extremely abundant resource; by weight 46% of the Earth's crust is made up of oxygen, present there as various oxides. For medical purposes, condensed or liquid oxygen is derived from filtered air by fractional distillation. At home, the end-stage COPD grandma will instead have a continuous low-flow oxygen concentrator device which works in a slightly different way. These devices use pressure swing adsorption, a form of molecular sieving. First, zeolite pellets (zeolites are a microporous aluminosilicate minerals) are exposed to pressurised air. The nitrogen in the air is adsorbed onto these pellets. The remaining pressurised gas mixture is mainly oxygen, and this is the gas sent to the patient via tubing. When the zeolite is saturated, the pressure in the reaction chamber is reduced and the nitrogen dissociates from the zeolite, venting into the atmosphere. As such, the device could just as easily be called a nitrogen (or argon) concentrator. Most home-based concentrators cycle like this every 20 seconds or so, storing a volume of ready oxygen gas in a chamber from which it is released in a controlled fashion. The realistic limits of performance for a domiciliary model seem to be somewhere in the realm of 5L/min, but they can be linked in parallel to produce higher gas flows.

Chemical relatives

Among pharmacological substances, oxygen has no equivalent relatives. It is structurally similar to its allotropes, monatomic oxygen and tri-atomic oxygen. O_1 is a dangerously reactive free radical found mainly in interplanetary space, and O_3 is ozone which is neither colourless (pale blue) nor odourless (the very name means "smelly", from the Greek "ὠζώ "). Singlet oxygen ($^1[O_2]$) is another species, a diatomic oxygen molecule which is in an excited quantum state that makes it more reactive and therefore slightly toxic (for example being responsible for some of the lung injury associated with hyperoxia). Apart from these, there are other species, like metastable tetraoxygen and superconducting metallic oxygen, but because these are present at pressures which are measured in gigapascals there will be no further discussion of them here.

Routes of administration

The administration of inhaled oxygen is classically via a variety of oxygen delivery devices which deserve a more detailed discussion elsewhere. In short, the main objectives of using such devices is to ensure that the rate of oxygen delivery and the concentration of delivered gas is well-matched to the patient's demands, so as to properly supplement any deficits.

Apart from these methods, oxygen can also be administered externally by flooding the ambient environment with it. When this is combined with an increased atmospheric pressure, one might describe this as hyperbaric oxygen therapy. The chapter at the end of that link is mainly concerned with giving a short memorable answer to Question 2 from the second CICM Part II paper of 2003, which is probably all that is required of CICM trainees. Detailed knowledge of this "good treatment in search of a disease" is probably not essential to exam success.

It suffices to say that the poor solubility of oxygen at normal atmospheric pressure can be defeated by increasing the pressure such that the dissolved fraction is sufficient to supply the metabolic needs of the organism. The upshot of this is that one can find oneself in a position where haemoglobin and the circulatory system in general become largely superfluous. *"We diluted the blood by extracting it via a tube in the femoral artery and infusing a clear fluid not containing haemoglobin into the femoral vein"*, wrote Boerema et al in 1959. These people diluted the bloodstream of lightly anaesthetised piglets with acellular plasma until the haemoglobin concentration was about 0.4g/L, a concentration at which urine would transition from rose to sauvignon blanc. They did this at 3 atmospheres of pressure with pure oxygen, i.e. at an FiO_2 of 300%. This method achieves an alveolar pO_2 of 2280 mmHg and the tissue oxygen tension approaches 400 mmHg. Under these conditions, these exsanguinated piglets remained alive for 45 minutes with intact corneal reflexes and reasonably robust spontaneous circulation. *"Recovery was uneventful after re-infusion of normal blood"*, gloated the authors.

More exotic methods of oxygen

Vladimir Negovski with Peter Safar in 1962, Moscow

administration exist. For instance, Vladimir Negovski (1961), the father of "reanimation" medicine in the former Soviet Union, made various attempts to resuscitate cardiac-arrested animals (and probably also human enemies of Communism) with blood which was mixed with an oxygen donor (usually hydrogen peroxide), injected in a retrodgrade fashion into the aorta of the subject. Since Soviet times this technique has genetally fallen into disuse. The modern equivalent would have to be the retrograde infusion of well-oxygenated blood via the arterial limb of the VA ECMO circuit.

Weirder still, disembodied transplant organs (though thankfully not any actual humans) have been *persufflated* with oxygen gas, the term being a portmanteau of "perfusion" and "insufflation". The technique has existed accidentally for some time since Rudolph Magnus (1902) first forgot to refill his perfusion fluid chamber, and the experimental cat heart became inadvertently persuffated with the oxygen he was using to pressurise his apparatus. The amazed author observed this error patiently for a further nine minutes, during which the gas-filled heart continued beating. Suszynski et al (2012) offer an extensive and highly detailed report on the work in this area, concluding that the barrier to widespread acceptance of this preservation technique is the totally reasonable concern that after such an organ is transplanted, the poor recipient will be laid to waste by a massive shower of gaseous emboli.

Absorption

Absorption of inhaled oxygen is rapid and usually driven by a concentration gradient, where the binding of oxygen to haemoglobin maintains a high gradient for diffusion across the impossibly thin alveolar membrane. This is the conventional mechanism of oxygen absorption and much is made of this mechanism in other chapters. There are other mechanisms, less known because their contribution to oxygen delivery is usually miniscule. In summary, the

total oxygen absorption under normal conditions is:

- Pulmonary absorption (250ml/min with 21% FiO_2, at rest)
- Cutaneous absorption (under 1ml/min at normal atmospheric pressure)
- Oral (and other) mucosal absorption (usually, nil)

Most of these are either trivial under all conditions, or only become relevant under specific conditions. For instance, the skin is the only other organ apart from lungs which is exposed to atmospheric oxygen, but because of its poor permeability and viable vascularity the fraction of skin-derived oxygen in the overall balance is minimal, particularly when the skin is dry. For the cutaneous absorption of oxygen to become anywhere near significant, Shaw and Messer (1930) had to crank up the heat and humidity to make the skin sweat. Even under optimal conditons, Stücker et al (2002) found that the whole-body oxygen flux from skin absorption was only 0.2-0.5 ml/m^2 per minute, which (with a normal human body surface area of around 1.7m^2) gives a total minutely oxygen supply of 0.90 ± 0.45 ml O_2. Considering that the pulmonary supply is around 250ml/min, this cutaneous absorption can be viewed as totally irrelevant to the whole-body oxygen economy. However, the rate of cutaneous oxygen absorption has much local significance, such that the top 0.25-0.40mm of epithelial cells are mainly supplied by absorbed oxygen and do not rely on the circulatory system for this. Down at that depth, moist skin will have a PaO_2 of around 50 mmHg purely from diffusion from the atmosphere.

This diffusive oxygen delivery may seem trivial and pointless, but for some tissues, it is a way of life. Famously, the cornea gets most of its oxygen in this fashion, as it would be optically inconvenient for it to be well-supplied with something as opaque as blood. The cornea is only about 0.5mm thick, and the cells thereof are rather metabolically quiescent, their major function being thinness and transparency, which means diffusion can meet their humble oxygen requirements reasonably easily.

Besides the skin and cornea, other tissues are capable of becoming gas exchange surfaces, if properly motivated. These methods, however, stray far from the bounds of medical convention, and should probably be left out of CICM exam answers. Forgotten examples are strewn across historic literature. The gastrointestinal tract, for example, has been an attractive alternative to the

lungs, made convenient by easily accessible ports of entry. From one end, Åkerrén & Fürstenberg (1950) tried to oxygenate asphyxiated newborns nasogastrically, observing that insufflation of 3-4L/min of oxygen into the stomach via a tube was safe and apparently effective at reviving initially cyanotic subjects. From the other end, Zaky et al (2012) were able to convince some patients with cirrhosis to undergo rectal insufflation with a mixture of oxygen and ozone (40% ozone), which increased the portal venous oxygen tension by 15mmHg (saturation from 82% to 90%). The authors were mainly interested in the effects of this on drug on hepatic drug metabolism, and fortunately did not make any attempt to actually oxygenate their patients in this fashion. Others (Lemus et al, 2006) eschewed the rectum in favour of the peritoneal cavity, which (with its markedly greater surface area and fewer organisms to compete for the oxygen molecules) turned out to be a much better gas exchange organ. Pigs with ARDS were insufflated with 5-8L/min of intraperitoneal oxygen for eight hours at a time, maintaining a low intraperitoneal pressure (5-6 mm Hg). Oxygenation was well maintained in spite of severe lung pathology.

Distribution of oxygen

Oxygen in the human body is a ubiquitous element. Neutron activation measurements in man (Wang et al, 1998, who for some reason used mainly men with AIDS) achieved a value of around 0.64, i.e. your body is 64% oxygen by weight. This, of course, is a physiologically unhelpful value because most of that oxygen is locked up in various molecules and is clearly not available to do good metabolic work.

There is, of course, a reservoir of oxygen which is available for metabolism. Unfortunately, the exact volume of that reservoir is difficult to report on, because every textbook you read produces a slightly different value. A more detailed whinge about this is recorded in the chapter on oxygen storage. Here, it will suffice to pick a set of values which seems authoritative. For lack of a higher authority, the following list comes from Kerry Brandis' *The Physiology Viva:*

Form of storage	O_2 stores on	O_2 stores after 100%

	room air (ml)	FiO_2 preoxygenation
As gas in the lungs (FRC)	270	1825
Bound to haemoglobin	820	910
Bound to myoglobin	200	200
Dissolved in tissue fluids	45	50

Metabolism and clearance

Oxygen is an essential component of normal metabolism and is required by all tissues, albeit unequally. If one needed to reproduce the fractional clearance of oxygen in an exam answer, one would probably reproduce these values:

Organ	Oxygen consumption (ml/min)	Oxygen consumption (% of total)
Brain	48	20%
Heart	25	10%
Kidneys	15	7%
Skeletal muscle	50	30%
Skin	5	2%

If the percentages are to be believed, these organs account for the majority of the total resting oxygen consumption in the human body. No matter which textbook one chooses, the numbers will be different, which adds a certain flavour of futility to the task of quoting any specific author. The difficulty in chasing precision in these values is discussed elsewhere. It will suffice to say that the textbooks differ depending on which papers they summarised, whether the values were human or extrapolated from animals, whether the subjects were anaesthetised, whether the measurements were taken in vivo or in disembodied organs, and a thousand other factors. In summary, in the exam, one would probably be safely able to write that the metabolism of oxygen takes place in all tissues but the main consumers are the brain, heart and skeletal muscle.

In the tissues, the main metabolic fate of oxygen is met in the mitochondria,

where cytochrome *c* oxidase enzymes of the oxidative phosphorylation pathway are responsible for 90% of the total body oxygen consumption. Oxygen is eliminated with zero-order kinetics, at a rate of approximately 200ml per minute for a normal-sized body at rest. The metabolites (CO_2 and water) are eliminated by ventilation and renal clearance.

Physiological effects of O_2 administration

These physiological effects consist of both the positive effects and the complications of oxygen therapy.

Oxygen-associated airway irritation

Oxygen is generally felt to be an airway irritant because the traditional method of administration has been to blow raw untreated wall gas at the patients. The harm was attributed to the physical properties of the gas - wall gas is too cold and too dry for the delicate mucosa, they said, and it results in drying and cracking, which progresses to epistaxis and unhappiness.

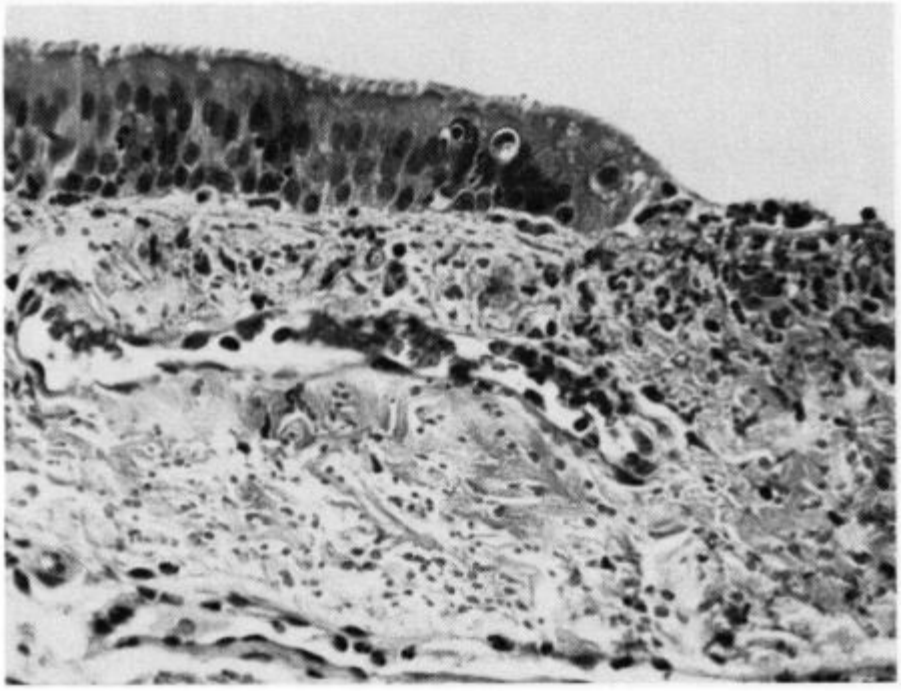

FIGURE 1. Trachea after six hours of breathing 100-percent oxygen. At left, respiratory epithelium shows intact cilia with early infiltration by polymorphonuclear leukocytes. There is ulceration of ciliated epithelium with exudation of polymorphonuclear leukocytes in lamina propria. Dilated blood vessel is present (hematoxylin-eosin, original magnification × 347).

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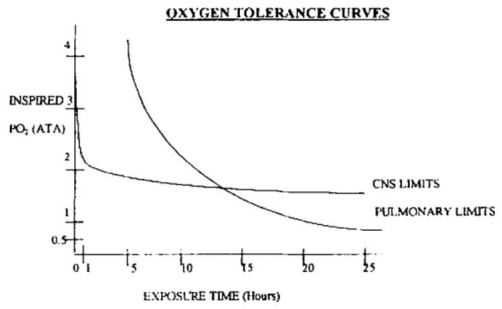
However, apart from the effects of being dry and cold, oxygen also appears to have a direct toxic effect on the mucosa of the airways. Specifically, it is said to cause tracheobronchitis, i.e. an inflammation of the lower airways. This complication of oxygen therapy is mentioned throughout literature, including in UpToDate. This belief appears to be based on a single dog study by Sackner et al (1976), who wafted warm humid oxygen (38℃, 100% humidity) over the tracheal mucosa of anaesthetised dogs. The investigators then scattered tiny Teflon disks over the tracheal mucus and filmed their movement at constant speed. The disks were slowed significantly after breathing 100% FiO_2 for a couple of hours - by around 50%. After six hours the trachea demonstrated clear evidence of inflammation - *"ulceration of ciliated epithelium with exudation of polymorphonuclear leukocytes in lamina propria"* was seen histologically.

It is unclear to what extent this occurs in humans. One year earlier to this study, Sackner et al (1975) were able to demonstrate something similar in

healthy humans but the experiment had significant methodological limitations - no histological analysis was possible and the two subjects who reported "bronchitis-like symptoms" may have done so because of the fact that their airways were repeatedly topicalised and bronchoscoped. Many intensivists confronted with these sorts of studies will become enraged and point to years and sometimes decades of experience with ventilated patients, swearing that they have never seen the clinical significance of hyperoxic tracheobronchitis. However, the savvy exam candidate will recognise the need to regurgitate the correct keywords. Thus, it would be important to mention oxygen-associated tracheobronchitis in a written answer.

Alveolar oxygen toxicity

If even warm humid oxygen irritates the relatively robust tissues of the trachea, then surely the delicate alveolar cells will fall apart completely from contact with highly concentrated oxygen. In some ways, this is true. The damage to cells from oxygen toxicity is generally the consequence of generating reactive oxygen species (O_2^-, $HO^{\cdot}$ and H_2O_2). Sustained exposure to oxygen will eventually overcome the beleaguered antioxidant scavenger systems (Heffner & Repine, 1989) and give rise to oxidative damage, changing the structure of macromolecules and therefore causing cellular dysfunction.



Cell death and inflammation ensue.

The toxic effect of pure oxygen on the lung parenchyma is known as the Lorrain Smith effect, after the pathologist who first demonstrated it in mice (Smith, 1898). After breathing an FiO2 of 70-80% for a week, half of the mice were dead, their lungs wooden with inflammatory changes and consolidation. The effect was much more rapid when the oxygen tension was increased by raising the atmospheric pressure: at about 1.3 atmospheres of pressure with 100% oxygen; *"the mice were at first very active, and ran about the chamber in a very lively manner,"* but were then found dead after 90 hours. *"The lungs were deeply congested, and sank in the fixing fluid"*, the author observed. No

microorganisms were found in the stained sections, apart from an occasional confused streptococcus. A directly toxic effect of oxygen was implicated.

This seems to be a concentration-dependent and time-dependent effect; the higher the concentration or the longer the time of exposure, the greater the harm. A nice graph from Chawla et al is reproduced here to illustrate the relationhsip of exposure time, FiO_2 and oxygen toxicity. FiO_2 below 50% (a PAO_2 of around 350 mmHg) appears to be associated with no significant damage over just about any period. In fact astronauts breathing 100% FiO2 at an extremely hypobaric atmosphere (around 250 mmHg atmospheric pressure) suffer no ill effects over many days. In contrast, humans subjected to hyperbaric oxygen for sustained periods have a relatively rapid onset of respiratory distress. A 1967 study by Clark & Lambertson (for the wicked-sounding Committee on Undersea Warfare, US Office of Naval Research) found that after 6 hours the subjects developed carinal irritation, and that respiratory distress ensued within 24 hours.

Inhibition of CO_2 transport by oxygen administration (the Haldane effect)

One of the effects which contributes to the hypercapnea resulting from oxygen administration to CO_2 retainers is the Haldane effect, explained in greater detail elsewhere. In short, as CO_2 tension is one of the factors which influences the affinity of haemoglobin for oxygen, so oxygen influences the affinity of deoxyhaemoglobin for CO_2. Deoxyhaemoglobin has a high affinity for CO_2, all the better to bind it in the deep hypoixc crevasses of the circulatory system. As O_2 increases, deoxyhaemoglobin binds it, becomes oxyhaemoglobin, and loses its affinity for CO_2. The previously safely haemoglobin-bound CO_2 now dissociates into the circulation, where it is free to wreak havoc on the central nervous system and acid-base balance. Aubier et al (1980) found this effect was probably responsible for at least 25% of the CO_2 increase associated with giving oxygen to CO_2 retainers. Presumably this effect is not as pronounced among non-COPD patients.

Role of oxygen in absorption atelectasis

The theory behind absorption atelectasis suggests that inhaling pure oxygen is inherently atelectato-genic because of the increased capacity of blood to carry away oxygen, as compared to nitrogen. The theory goes, that oxygen in lung

units which are insufficiently well ventilated (or frankly obstructed and isolated by sputum plugs) will be rapidly absorbed by the circulation, and that volume loss will result. Lung units where respiratory gas entry is slower than circulatory gas removal will therefore lose volume. If one has filled that lung unit with pure O_2, the volume loss will be absolute (as 100% of the volume is oxygen, and 100% of the oxygen is carted away by haemoglobin).

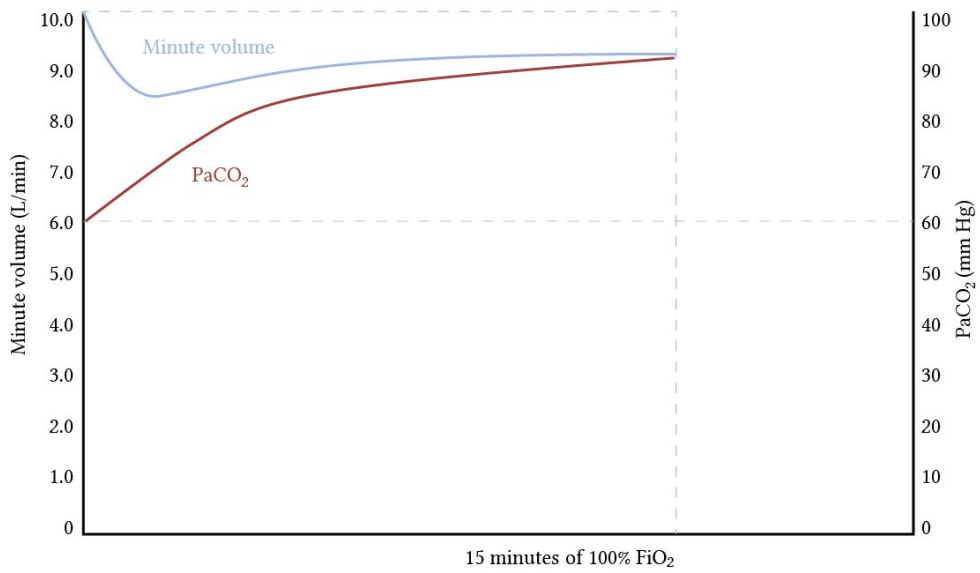
This theory originates probably in the late 1950s, though many later authors have modeled it (eg. Joyce & Baker (1993) used 1993-era computers to created a mathematical simulation of it). Some of the first papers on the subject (eg. Rahn & Dale, 1952) produced results which suggested that the rate of atelectatic collapse was higher with higher fractions of inspired oxygen.

It sounds great in theory, but in practice it is unclear whether this contributes significantly to the overall atelectasis which occurs in mechanically ventilated patients. If it did, then it would stand to reason that ventilation with some minimal FiO_2 (i.e. adding extra nitrogen) should protect against atelectasis in perioperative patients, whereas the same Joyce & Baker team (1995) demonstrated experimentally that it does not. An even earlier CT-based imaging study by Brismar et al (1985) demonstrated that the size of the crest-shaped densities which appeared in the lungs of mechanically ventilated patients did not vary no matter how high they cranked up the FiO_2. In short, it seems the contribution of this process to atelectasis is probably overhyped, unless the lung unit is completely blocked off (in which case it matters very little which gas it's filled with).

Effects of oxygen administration on respiratory drive

Among many otherwise reasonably well educated people there exists the belief that CO_2 retention in COPD patients develops because these chronically hypoxic people are dependent on their hypoxic respiratory drive for their minute ventilation. This myth originated probably with Donald et al (1949), who attributed the coma of their obtunded CO_2 retainers to this mechanism. Being accustomed to having a high CO_2, Donald et al reasoned, these patients would have had their hypercapneic respiratory drive homeostatically reset to some ludicrously high point, and would therefore be relying on their hypoxic drive to maintain their minute ventilation in day-to-day life. However, there are several problems with this interpretation.

Firstly, it is unlikely that increasing these people's PaO_2 back to a normal range (over 75 mmHg) contributes much to their hypoxic drive suppression, as to completely silence the hypoxic drive a PaO_2 of 200 mmHg is required (Kozlowski et al, 1971). Secondly, we have empiric evidence that giving oxygen does little to the minute ventilation of CO_2 retainers. This is best represented in a graph which reinterprets data from a highly cited article by Aubier et al (1980).



Aubier et al (1980) got a bunch of known CO_2 retainers mid-exacerbation and gave them oxygen. They didn't just give these people a little extra sniff of oxygen, they totally saturated them with 100% FiO_2 via a plethysmograph mouthpiece. The hypoxic drive would have been totally abolished with an average PaO_2 of around 225 mHg. The minute volume remained essentially unchanged (it went from an average of around 10.0L/min to an average of around 9.0L/min). At the same time the CO_2 went from 60 to 90 mmHg. If one were *completely apnoeic*, one might expect a rate of CO_2 rise of around 3mm per minute, which would have raised the $PaCO_2$ from 60 to 105 mmHg. In other words, in spite of the fact that the patients continued breathing at approximately the same minute volume, their ventilation worsened as if they had decreased their minute volume by two-thirds. Clearly, mechanisms other than the respiratory drive suppression are responsible for the CO_2 retention in hyperoxygenated COPD patients.

Effects of oxygen on pulmonary circulation

The *absence* of oxygen is a potent pulmonary vasoconstrictor. This was first confirmed in the late 1940s, when instruments for measuring pulmonary pressures became available. For instance, Motley et al (1947) got five healthy males to breathe 10% FiO_2 for a while (a $PaO_2$of around 35-40 mmHg, depending on humidity and the CO_2). These people consented to having their pulmonary arteries catheterised.

6. *Pulmonary artery blood pressure*, mm. Hg		
Systolic	21.9	35.1
Diastolic	6.0	13.0
Mean	13.1	23.0

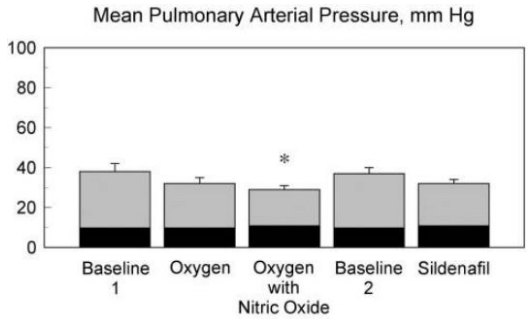
The numbers on the left are on room air; those on the right are after breathing 10% FiO_2 for ten minutes. As one can see, the PA systolic pressure increased by about 13mmHg, mean PAP increased by 10 mmHg and the resistance almost doubled (though remaining relatively low). These volunteers had oxygen saturation around 77-80% at the end of the ten minutes, and were hyperventilating. After one minute of breathing room air again, PA pressures returned to normal, which gives you a bit of an idea of how reactive these smooth muscles are.

Why does this happen, and what drives it? A.F. Fishman (1976), Weir et asl (1995) and most recently Sylvester et al (2012) offer excellent accounts of the historic path we took to discover the mechanisms involved in hypoxic pulmonary vasoconstriction. It was initially thought to be a mechanism related to the activity of the sympathetic nervous system because adrenaline was seen to cause pulmonary vasoconstriction, and because sympathetic overactivity was observed in laboratory models of severe hypoxia. However, Goldring et al (1964) were able to demonstrate that hypoxic pulmonary vasoconstriction occurs in the absence of any major rise in systemic catecholamine levels, and that the dose of noradrenaline required to vasoconstrict those vessels is far in excess of what is usually seen in severe hypoxia. Much later, in 1987, von Euler & Liljestrand were able to demonstrate that this vasoconstriction is not global but regional, *"leading to an adequate distribution of the blood through the various parts of the lungs according to the effeciency of aeration."*

Regional pulmonary responses to hypoxia are due to the inhibition of an outward potassium current and activation of an inward sodium current, which depolarises the membrane of pulmonary vascular smooth muscle cell, causing them to contract. The systems described by Sylvester et al (2012) are so

ridiculously complex that an entire textbook could be dedicated to them. On page 413 of the paper, a massive flowchart diagram of the intracellular mechanisms is offered, with enough arrows to discourage any reader. The take-home message is that slightly different mechanisms and sensitivities to hypoxia are present in different pulmonary arteries, and even in different cells within the same vessel, creating a "mosaic" of hypoxia-responsiveness.

So, if oxygen has this effect, will it act in the same way as prostacycline or nitric oxide if you have severe pulmonary hypertension? Turns out, probably not, or at least not by much.



Ronald Day (2015) performed experiments in 13 individuals with chornic hypoxic pulmonary hypertension who happened to be undergoing right heart catheterisation. Measurements were taken with different concentrations of oxygen and then also with well-established pulmonary vasodilators like sildenafil and nitric oxide. The patients were fairly hypoxic at baseline (PaO2 was around 6_2 mmHg on average). With 100% oxygen, pulmonary arterial pressures did not change dramatically. Nor for that matter with the other drugs. The key take home message here is probably that the chronciity of pulmonary hypertension makes these crusty wooden vessels unlikely to respond to anything. Something similar was demonstrated in a much older study which - instead of using patients with existing pulmonary hypertension - *induced it* in eight athletic male volunteers, who apparentl;y had nothing much to do for a few weeks. Groves et al (1987) decompressed these people in a hypobaric chamber for *forty days*. The barometric pressure in the chamber was 240 mmHg, approximately equal to the summit of Mt Everest. Resting pulmonary arterial pressure in these people increased from 15 mmHg to 34 mmHg, and did not change very much with 100% FiO_2. In summary, though hypoxia cause regional pulmonary vasoconstriction and this is relieved by normoxia, hyperoxia does not have a significant pulmonary vasodilator effect.

Effects of oxygen on cardiac function and systemic circulation

Oxygen in the systemic circulation acts as a vasopressor, increasing the blood pressure and decreasing the heart rate and cardiac index. The effect is not massive: for example, from breathing room air to 100% FiO_2, the heart rate decrease is by about 10 beats per minute. These data come from Daly & Bondurant (1962), who were able to convince fifteen normal males to undergo indocyanine green dye dilution-based cardiac output studies before and after breathing 100% oxygen. The normal males also ended up with slightly higher blood pressure (MAP went from about 94 mmHg to about 95 mmHg on average, which hardly seems important). The peripheral vascular resistance, measured in oldschool "PRUs" (mmHg·min·mL^{-1}), went from 16.3 to 18.5 U, or from 1,300 to 1,480 dynes·sec·cm^{-5}. Cardiac index dropped from 3.0 to 2.7 L/min/m_2, again a trivial effect.

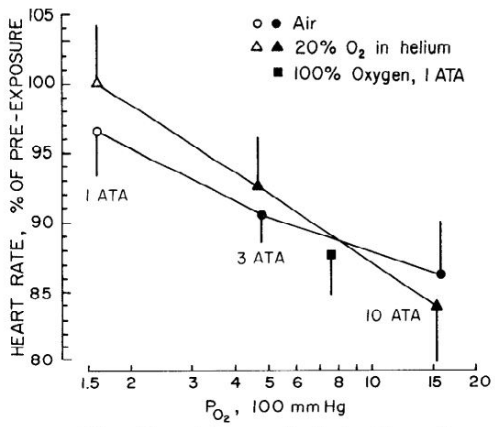


FIG. 4. Effect of O_2 partial pressure (P_{O_2}) in breathing medium on heart rate. Each *point* represents mean ± SE for 6 rats.

The person who grew up with Mythbusters will then ask, "if [this much] oxygen causes [this much] effect, then surely *more* oxygen must produce *more* effect?" In fact, it does, but not by much. Even at some multiples of normal atmospheric pressure the effect is small. In their chapter for the *Handbook on hyperbaric medicine,* Mathieu et al (2006) quote numerous historic studies to support this. For instance, the graph reproduced here comes from one of their references (Shida & Lin, 1981). These authors could not find human volunteers (and rats were easier to convince), but others did (French SCUBA divers, Molenat et al, 2004) and in any case the data can probably be extrapolated to all mammals. Even at 10 atmospheres of 100% oxygen (that's an PAO_2 of over 7,000 mmHg) the rat heart rate decreased only by 15% from baseline. Systolic pressure in the French divers increased from a baseline of 124 mmHG to 130. As a vasopressor, that makes oxygen extremely weak; increasing the dose by ten times produces only at most a 15% increase in effect.

What is the mechanism of these changes? Hyperoxic vasoconstriction has

generally been blamed on reactive oxygen species. McNulty et al (2005) found that the increased concentration of ROS accelerates the rate of oxidative degradation of nitric oxide in the endothelium. The result is an increase in vascular resistance. The heat rate then decreases as a consequence of the baroreceptor response to the increased mean arterial pressure. The cardiac index presumably decreases due to the lower heart rate and higher afterload, although McNulty et al (2005) also found that coronary blood flow can decrease by as much as 30% in patients with stable coronary artery disease, and that alone could account for a decrease in cardiac output. This has implications for the pulmonarily oedematous grandma with an LAD infarct, on the ambulance stretcher with a non-rebreather oxygen mask.

Effects of oxygen on the cerebral circulation

Hyperoxia decreases cerebral blood flow. One might surmise this is by the same mechanism as the nitric oxide-related systemic vasoconstriction. In 1948, Kety & Schmidt found the decrease was by about 13% when breathing 100% normobaric FiO_2. In a cruel-sounding "brain missile wounding" cat model, Torbati & Carey (1989) found that this vasoconstrictive effect is exaggerated in an injured brain. Conversely, hypoxia (breathing 10% FiO_2) was associated with increased cerebral blood flow (by 35%). Davis et al (2009) confirm that both hypoxia and hyperoxia are associated with poorer outcomes in severe traumatic brain injury, though this was a registry-based analysis rather than a trial.

Effects of oxygen on central nervous system function

So, a decreased cerebral blood flow is observed in healthy volunteers at normobaric hyperoxia, but are they any worse for it? Will they misbehave during a diving operation, or trash their ICU cubicle? This is obviously of some importance to non-medical fields which expect hypoxic and hyperoxic subjects to perform complex tasks. Obviously hypoxia is going to have negative cognitive effects; Malle et al (2016, for *Aerospace medicine and human performance*) found that hypoxia results in EEG slowing and decreased working memory.

Normobaric hyperoxia seems to have the opposite effect, but the literature is conflicting. Scholey et al (1999) found hyperoxic volunteers more adept at word

recall and simple reaction-time tasks, suggesting that oxygen is something of a performance-enhancing drug. Seo et al (2007) only gave 35% FiO_2 and also found an improvement in verbal learning ability, associated with some EEG changes. On the other hand, Sheng et al (2017) demonstrated the same sort of changes in EEG activity, but the authors instead suggested that these should result in memory *impairment* instead. *"EEG rhythms associated with cognitive processing, such as the α and β bands, showed a diminishment under hyperoxic conditions"* they said. In summary, the jury is still out. Though hyperoxia clearly affects the EEG, it is unclear whether it has any sort of beneficial or deleterious cognitive effect, and under which conditions they manifest (delirium, sepsis? Dogfight, aircraft cockpit?).

In contrast, hyperbaric hyperoxia clearly has significant and terrible neurological effects. As Lorrain Smith is known for the pulmonary toxicity effect of oxygen (Smith, 1898), so Paul Bert is known for the "Paul Bert" effect, which is the seizures associated with hyperbaric oxygen toxicity. Meticulously recorded bird experiments record that this typically occurs at approximately 4 atmospheres of pressure.

2.10 Dyspnœa.
2.19 Dyspnœa increasing. Tension raised to 342 %.
2.25 Tension raised to 365 %. Bird quiet. Co-ordination difficult.
2.35 Tension raised to 408·9 %. Dyspnœa.
2.40 Convulsions. Apparatus burst.

It is not clear why Bert, in the scientific ethical vacuum of 19th century Paris did not use mammals to perform his experiments. Surely mice (or volunteer Frechmen) would have been more ubiquitous and easier to handle than larks, owing to their being unable to fly. Fortunately from the vantage point of the modern day we can benefit from thousands of poorly controlled human experiments. For instance, Hampson et al (2003) analysed the outcomes of 20,328 hyperbaric oxygen treatments performed from 1992 to 2001, finding a seizure rate of 1 in 3,388 (using pressures usually no greater than 2.4 atmospheres). Plafki et al (2000) gives some risk factors which predispose a person to such seizures: hypercapnia, hypoglycaemia, hyperthyroidism, fever, penicillin use, disulfiram, and of course epilepsy. Judging from the animal studies, this effect is both dose and time dependent (i.e. only a short time at high pressure is required to produce seizures). The mechanism for these remains to be established; modern authors (eg. Brian et al, 2001) cannot expand

very far beyond the speculations offered by Lambertsen et al (1953), who blamed the seizures on reactive oxygen species, catecholamines and changes in cerebral circulation.

Effects of oxygen on electrolyte composition of body fluids

In summary:

- Blood glucose decreases
- Serum sodium decreases
- Potassium increases

Gupta & Sharma (2000) looked at the biochemistry of diabetic and non-diabetic patients undergoing hyperbaric oxygen therapy and found that after 50 minutes at 250% of atmospheric pressure the patient's BSL and sodium were lower, and potasium was slightly higher (from 4.2 to 4.5). These changes could hardly be described as clinically significant. The authors felt that this effect might be due to the increased activity of the Na^+/K^+ ATPase, but were unable to support that with anything.

Impairment of erythropoiesis by oxygen

Oxygen levels regulate erythropoiesis and influence the handiling of body iron. Volker Haase (2010) describes these processes in great detail. In summary, both the synthesis of erythropoietin and the expression of the receptor for erythropoietin are induced by hypoxia, a process which seems to be mediated by the "hypoxia-induceable factor" HIF-1α protein. With hyperoxia, the serum level of EPO declines. The drop is not massive- Kokot et al (1994) found that even when breathing 100% oxygen the EOP levels decline by a maximum of 40% or so, after 6 hours. In other words, maximal hyperoxia at normal atmospheric pressure is not enough to completely shut off erythropoiesis.

Effect of oxygen on the immune system

Hyperoxia has an immunosuppressant effect. Baleeiro et al (2003) inoculated the lungs of hyperoxic mice with *Klebsiella pneumoniae* and found that their alveolar macrophages were so stunned by the oxygen that mortality among them increased significantly (from 50% to 90%). The macrophages were rendered lazy and useless, neither inclined to save the mice by killing the

Klebsiella nor to participate in the experiment by phagocytosing little plastic beads. Waisman et al (2003) also observed decreased granulocyte rolling and diapedesis in hyperoxia following mesenteric ischaemia, which they interpreted as a good thing (less inflammation, etc). In summary, hyperoxia probably decreases the activity of the immune system sufficiently to have some sort of clinical relevance.

Effect of oxygen on anaerobic organisms

Anaerobic bacteria fail to thrive at normal atmospheric oxygen tension, let alone the supersaturated tissues of a patient in a hyperbaric oxygen chamber. From this, it follows that hyperoxia should slow or reverse the progression of severe anaerobic infections. Brummelkamp et al (the et al included Boerema, 1962) were probably the pioneers of this. The observation that necrotising infections improve with hyperbaric oxygen was further supported by studies such as Riseman et al (1990) whose patients required fewer debridements and had improved mortality. It is unclear whether this is because the patients have improved healing, less inflammation (or more?), better wound perfusion or direct antibiotic effects of oxygen. Probably the latter plys a minor role. Rolfe et al (1978) found that the degree of "aerotolerance" in anaerobic organisms was quite variable. For example, *Peptostreptococcus anaerobius* from a normal healthy vagina didn't last longer than 45 minutes, whereas *Clostridium perfringens* strains were still going strong after 72 hours of exposure.

Accepted indications for the use of oxygen

Correction of hypoxemia

This is one of those situations where the nerdy distinction between *hypoxia* and *hypoxemia* becomes relevant. The main difference is that hypoxemia is a low oxygen content in the blood, whereas hypoxia is the process which has caused hypoxemia. Supplemental oxygen administration usually cannot correct the hypoxia, but it can at least address the hypoxemia, delaying death and improving the cosmetic appearance of the arterial blood gas. There are numerous permutations of this (eg. use of oxygen in carrdiac arrrest, in shock, trauma, sepsis, and so forth) but because all of these

indications use oxygen for the same sort of technical reasons it seems unreasonable to elaborate on them. In case one needs references for the various hypoxemia-related uses of oxygen, one will be able to find them in the BTS guideline (page i41 onward).

Displacement of carbon monoxide from haemoglobin

Both isobaric and hyperbaric oxygen has been used to treat carbon monoxide toxicity. The concentration of carbon monoxide required to cause toxicity is quite low; an FiCO of around 1% is rapidly fatal, producing a carboxyhaemoglobin concentration of over 70%. Because of the high affinity of carbon monoxide for haemoglobin, more than the normal amount of oxygen is required. A higher concentration of lower-affinity oxygen will be better able to compete with the relatively low concentration of high-affinity carbon monoxide. Mark Goldstein (2008) reports that the half-life of carboxyhaemoglobin decreases from 300 minutes on room air to 90 minutes on 100% isobaric oxygen, and to 30 minutes with hyperbaric oxygen.

Denitrogenation of air-filled cavities

The use of high oxygen concentration has been used to increase the gradient for nitrogen to be absorbed into the blood. This has multiple possible uses. Essentially, any gas-filled cavity should shrink with this strategy. A by-no-means-exhaustive list of such cavities is offered here as an example:

- Air embolus
- Pneumothorax
- Pneumomediastinum
- Pneumoencephaly

How rapidly will the pneumothorax resolve, one might ask? This is variable. Zierold et al (1999) punctured the lungs of 27 white rabbits and recorded that at 60% FiO_2, their pneumothoraces resolved radiologically within 40 hours or so, rather than 110 hours on room air.

Situations in which hyperoxia is demonstrably harmful

There are several scenarios in which "individualised" oxygen therapy (i.e. targeting of a reasonable oxygen saturation value) is clearly superior to the random abuse of high FiO_2. An excellent 2017 article by J.L Vincent is a good starting point for reading about this. In it, there is a massive two-page table of various studies which had demonstrated some harm or another as the result of hyperoxia. Instead of elaborating so extensively, the conditions made worse by hyperoxia are listed below:

- Ischaemic stroke
- TBI
- Subarachnoid haemorrhage
- Post-cardiac arrest coma
- Myocardial infarction
- Sepsis
- Neonates (retinopathy)
- Bleomycin and paraquat (lung fibrosis)

Previous chapter: Carbon dioxide and oxygen response curves

Next chapter: Physiological effects of hyperoxia

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